Urinary Tract Infections

Problems in Medical Management

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• The lesion principally responsible for chronic, or recurrent, urinary tract infection is a focus in the interstitial tissue of the kidney. Most cursory antimicrobial therapy suppresses the manifestations of lower urinary tract involvement but does not eradicate the renal focus. In order to cure rather than merely suppress the infection, it is imperative that, as early as possible, steps be taken to isolate and identify the etiologic microorganism and to determine its sensitivity to antimicrobial agents. Based on this information sufficient amounts of drug should be given for an adequate period (probably at least two weeks) to eradicate the infection within the renal tissue. Such a program would tend to reduce the number of cases in which irreversible renal failure develops from chronic pyelonephritis.

INFECTIONS of the urinary tract are second in frequency only to upper respiratory tract infections, and often more severe. In a series of 3,000 unselected autopsies active "septic infection" of the urinary tract was noted in 4.8 per cent.[12] Before attempting to discuss the management of these disorders it may be desirable to outline their natural history. It had long been suspected that some connection existed between the acute, brief episodes of manifest urinary tract infection and the ultimate development of renal failure. The long term studies of individual patients by Longcope and Winkewerder[9] suggested that often a process of inflammation smouldering below the levels of manifest symptoms connected the episodes of clinically evident pyelonephritis and resulted in progressive scarring and fibrosis of renal tissue. That such a progressive course is by no means inevitable is indicated by the finding[11] of the scars of healed pyelonephritis in nearly 14 per cent of 1,000 consecutive autopsies at the Boston City Hospital. Pyelonephritis thus often heals spontaneously. However, occasionally it may be a very malignant disease with rapid progression toward renal failure, as in papillary necrosis occurring in nearly one fifth of diabetic patients with pyelonephritis.[10]

The hypothetical life history of a female with urinary tract infection (Chart 1) will serve as illustration. In early childhood there occurred a febrile episode recognizable as acute pyelonephritis, perhaps associated with some minor anatomical anomaly of the urinary tract. Or possibly even the initial episode was mild and not associated with clear-cut symptoms referable to the urinary tract. Subsequently the process was quiescent or only minor flare-ups occurred during adolescence. Shortly after marriage the patient had an attack of "honeymoon pyelitis." During pregnancy "pyelitis" developed in the second or third trimester. There was no toxemia and a normal delivery was followed by a period of quiescence and apparent health. Both in childhood and in adult life the infection might spontaneously heal completely. (More frequently, however, there are continuing attacks of pain in the flanks, intermittent pyuria, dysuria and urinary frequency with little fever or other systemic manifestation. During symptom-free periods bacteria may often be detected in the urine.) Up to this time the kidney function was quite unimpaired. Then nitrogen retention, proteinuria, and perhaps an associated rise in blood pressure developed. Subsequently, the progression of renal failure was exceedingly rapid, or perhaps it developed slowly over many years.

Looking at urinary tract infection as a long-term problem and not as a series of brief, unconnected episodes, it becomes clear that the basic, important lesion is not an infection of the urine, or of the duct

LIFE CHART OF A FEMALE PATIENT WITH URINARY TRACT INFECTION

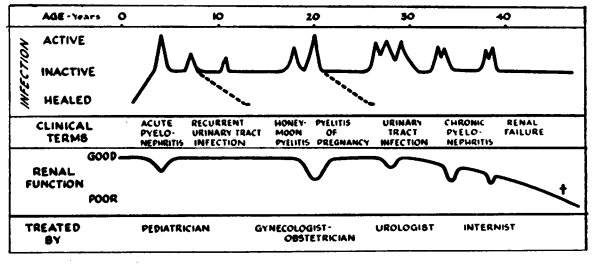

CHART 1

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Presented before the Section on Pediatrics, at the 82nd Meeting of the California Medical Association, May 24-28, 1953.

Based on a cooperative study with Drs. James Hopper, Jr., and Frank Hinman, Jr., and supported in part by a grant-in-aid from Burroughs Wellcome & Co., Tuckahoe, N. Y. Dr. Donald R. Smith gave valuable advice.

system from glomerulus to bladder, but infection of the interstitial tissue of the kidney.[2, 9] Regardless of the route (whether hematogenous, lymphogenous, or urogenous) by which the infecting bacteria reach the kidney, it is the chronic inflammation within the parenchyma with destruction and fibrosis of nephrons that determines chronicity, resistance to treatment, and ultimate outcome. The management of urinary tract infection and its problems must be considered from this point of view. It was recently stressed by Birchall[1] that one of the difficulties in over-all management is the discontinuity of attack, each episode being treated as an isolated event by a different physician (pediatrician, gynecologist, urologist, internist). For optimal handling of the patient a different, long-term approach is necessary.

To cover all aspects of the disease the management of urinary tract infection falls properly into three categories: (1) Correction of structural abnormality of the tract. (2) Treatment of the infective process. (3) Palliative management of renal failure and associated disturbances. The first is in the province of the urologist; investigation and correction are carried out by specialized methods. The third, the treatment of renal insufficiency, hypertension and other consequent conditions, requires careful attention to detailed management of fluids, electrolytes, diet and other such factors. Expert management along these lines will often keep a patient alive to receive antibiotic therapy. This presentation is concerned with the second of the three categories of management mentioned above, treatment of the infectious process, for by optimal treatment organic damage to the kidney may be prevented.

A planned attack upon the infective process includes a specific etiologic diagnosis, selection of appropriate antimicrobial agents, administration of them in adequate doses for a sufficient time, and prolonged follow-up to establish cure with certainty. It is proposed to consider each of these elements in their logical sequence. Some technical detail will have to be included since, quite commonly, minor "unimportant" features are omitted, contributing to therapeutic failure.

ETIOLOGIC DIAGNOSIS

The key to etiologic diagnosis is a careful examination of the urine. Urine specimens must be collected, before chemotherapy is started, by methods suitable to exclude contamination from the outside (catheterization in females; clean, voided specimens in males), and must be examined promptly lest bacteria either die or multiply. Complete bacteriological examination includes the following procedures:

1. Examination of a stained smear of urine. (Ordinarily bacteria will be noted only if the number exceeds 10,000 per milliliter.)

2. Qualitative culture to isolate the different kinds of bacteria present.

3. Quantitative culture to estimate the number of bacteria in fresh urine. This is essential because the voided urine of normal persons may contain a few bacteria, perhaps up to 500 per milliliter. These organisms originate in the normal urethral flora or in occasional lymphatic transport from other viscera to the lower urinary tract. Their presence does not ordinarily denote disease. Larger numbers of bacteria, in excess of 1,000 per milliliter, even in the absence of pus cells, are indicative of urinary tract infection.

4. Special studies, when indicated, to detect anaerobic bacteria, tubercle bacilli, fungi, or pleuropneumonia-like organisms.

THERAPEUTIC AGENTS

The principal reason for isolating the etiologic microorganisms is not the academic one of specific diagnosis for its own sake, but the urgent need to determine the antimicrobial drug most likely to be effective against the particular microorganism. What with the large scale use and misuse of antibiotics, many patients now harbor bacteria which are resistant to one or several drugs. The rapid, qualitative "disc" method of antibiotic sensitivity testing, in spite of many inadequacies, often gives a valuable lead as to what drugs are likely to inhibit the infecting microorganisms, and, of equal value, what drugs should not be used because the organisms appear to be resistant to them. While this, admittedly, is only a partial answer to the problem, such an answer can be obtained rapidly and cheaply. If a proper urine specimen is submitted to the laboratory in the afternoon, the physician can be informed the next morning as to the kinds and the number of bacteria present and the drugs to which they are resistant or sensitive. With good collaboration between physician and laboratory these results can give valuable guidance to therapy.

Most antimicrobial drugs are excreted largely through the kidneys and concentrated in the proximal convoluted tubules. Consequently the drug concentration in the urine tends to be several times that present in body fluids, blood, or tissues. For this reason it has become customary to use small, so-called "urinary doses" of most antimicrobial agents which result in urinary concentrations sufficient to inhibit most infecting microorganisms. Thus 0.5 gm. of a sulfonamide taken four times daily results in a concentration of approximately 50 mg. of the drug per 100 cc. of urine, but would obviously not

be an adequate amount to produce systemic tissue levels of the drug. If such "urinary doses" of antimicrobial drugs are taken for a few days the urine is usually "sterilized" quite promptly, and the symptoms, particularly of lower urinary tract involvement, subside rapidly. Cultures taken during therapy and immediately thereafter are frequently negative. This may lead to the belief, often unwarranted, that the patient has been "cured."

It has been said already that in pyelonephritis there is primarily infection in the interstitial tissues of the kidney, and that the involvement of the urinary passages is often secondary. The condition of the urine may be only a manifestation of the neighborhood involvement of renal tissue and inflammation of the lower tract. On the other hand, the urine may be sterile and contain no pus cells while there is active and progressive infection and inflammation in the renal parenchyma. Logically, therefore, treatment should not be limited to sterilization of the urine, which can be readily accomplished, but should be directed to eradication of the renal infection. From this standpoint the use of "urinary dosage" of antimicrobial agents, and of "urinary antiseptics," such as methenamine, which function only in an environment of acid urine, seems quite perfunctory. Such therapy provides symptomatic relief, without attacking the source of the trouble. This situation in pyelonephritis could be compared to that well-recognized in bacterial endocarditis.[4] If a patient with endocarditis is treated with small doses of a drug that can inhibit the infecting organism, the symptoms of infection (fever, embolic phenomena, fatigue) may subside and no organisms grow on a culture of blood. However, soon after such treatment is discontinued, relapse occurs, because the focus of active infection within the vegetation on the heart valve has not been eradicated. Such patients are cured only if a drug known to kill (and not merely inhibit) the infecting organism is given in adequate dosage for a sufficient length of time to penetrate the vegetation, eradicate most viable organisms and permit solid fibrosis to encapsulate the remaining few central bacteria so that they will be unable to proliferate again when chemotherapy is discontinued.

It would seem logical to apply similar principles in the treatment of urinary tract infection when renal involvement is evident. Following isolation of the infecting microorganism from the urine, it should be subjected to antibiotic sensitivity tests that measure not only the inhibitory but also the killing capacity of the drug.[4, 6, 8] Then, using drugs, singly or in combination, that are lethal to the infecting bacteria in the test tube, "systemic" rather than "urinary" doses should be given — that is, amounts sufficient to saturate tissues with drug levels capable of eradicating the bacteria. This drug regimen must be continued long enough to permit sterilization of tissues, probably for more than two weeks. Subsequently cultures should be obtained for at least three months, to make certain infection does not recur. It is probable that with such a course of treatment generally carried out, the rate of permanent cure would be greatly increased and that the number of cases in which disease progressed into renal failure owing to chronic pyelonephritis would be diminished.

However, this ideal — possibly idealistic — approach to treatment is not without flaws, which pertain to the properties of antimicrobial drugs and to characteristics of chronic pyelonephritis.

Most cases of pyelonephritis are associated with Gram-negative bacteria. The principal drugs active against such organisms, like sulfonamides, aureomycin, chloramphenicol, or terramycin, are inhibitory rather than bactericidal. They often "sterilize" the urine promptly, but probably do not eradicate foci of infection in the interstitial tissue of the kidney, just as they do not cure bacterial endocarditis.[4] Streptomycin is bactericidal but drug-resistant forms emerge so quickly that this drug cannot be usefully employed alone for more than four days in bacterial infections, a time too short to permit eradication of an interstitial focus. Combinations of drugs may occasionally be used for this purpose but selecting them in the laboratory still remains a laborious procedure, and an indiscriminate mixture of drugs is likely to be ineffective. Available information about antibiotic combinations has been summarized elsewhere.[6]

Among other drugs, polymyxin B would appear to offer some hope. This agent is highly bactericidal for many Gram-negative bacteria,[7] including many resistant to other drugs. Recent studies indicate[3] that in persons with good renal function doses up to 2 mg. per kilogram of body weight per day for 14 days are tolerated without significant evidence of nephrotoxicity. There are, however, unpleasant side actions (local pain at injection site, neurotoxic effects) which make more prolonged use difficult to tolerate. In selected cases of acute pyelonephritis in children, polymyxin B resulted in complete eradication of infection.[5, 13] When adults with known long-standing pyelonephritis, but good renal function, were treated with polymyxin B for two weeks in doses of 1.5 to 2.2 mg. per kilogram per day, cultures of the urine promptly became negative for bacterial growth and remained so for from one to six weeks after treatment. However, in many cases the original bacteria reappeared in the urine eventually. This suggests strongly that the fibrosing in-

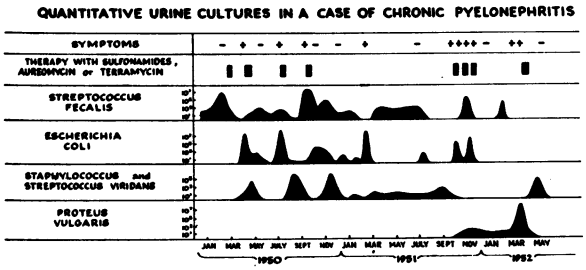

CHART 2

fectious focus in the renal tissue is not readily accessible to drugs and that treatment would have to be much more prolonged than seemed feasible with polymyxin B.[3]

It is a common experience among those who treat many patients with chronic urinary tract infection to observe the disappearance of the prevalent bacterial species under treatment with one drug, and its replacement with another species, usually resistant to the agent being used. The origin of these "superinfecting" organisms is not known, but it seems that they usually appear when a prevalent bacterial population is suppressed by antimicrobial therapy. However, that event merely seems to increase the opportunity for multiplication, and perhaps establishment of a different bacterial species. When quantitative studies of the growth of organisms on cultures of the urine of persons with long-standing urinary tract infection are carried out, spontaneous changes in flora are sometimes observed as shown in the detailed bacteriological study summarized in Chart 2. While it seems definite that the patient initially harbored an enterococcus infection in the kidney parenchyma, other organisms appeared at times in the urine, and on certain occasions enterococci could not be found, but only the "superinfecting" bacteria descended from the kidneys.

It might even be conjectured that some abnormality of lymphatic connection, or of urinary flow, might predispose such a person to continuous seeding of the kidneys with enteric organisms; that once a given bacterial species was established, other organisms might have less opportunity of settling down and multiplying; but, if the first species were suppressed by drugs or change in environment, new varieties of bacteria might readily supplant it. While this is pure speculation, it lends an additional discouraging note to the problem of treating chronic, long-standing urinary tract infection and emphasizes the urgency of definitive diagnosis and thorough treatment as early as possible, when permanent eradication of infection is frequently feasible by present-day methods.

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